ALEXANDER L. BRAINERD (Bar No. 42722)
MICHAEL K. PLIMACK (Bar No. 133869)
CHRISTINE SAUNDERS HASKETT (Bar No. 188053)
SAMUEL F. ERNST (Bar No. 223963)
HELLER EHRMAN WHITE & McAULIFFE LLP
333 Bush Street
San Francisco, CA 94104
Telephone: (415) 772-6000
Facsimile: (415) 772-6268

MARK S. PARRIS (*Pro hac vice*)
LEONARD J. FELDMAN (*Pro hac vice*)
KALAI LAU (*Pro hac vice*)
HELLER EHRMAN WHITE & McAULIFFE LLP
701 Fifth Ave., Suite 6100
Seattle, WA 98104
Telephone: (206) 447-0900
Facsimile: (206) 447-0849

Attorneys for Defendant and Counterclaimant
MULTILYTE LTD.

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

AFFYMETRIX, INC., a Delaware corporation, Plaintiff and Counterdefendant, v. MULTILYTE LTD., a British corporation, Defendant and Counterclaimant.	Case No.: C-03-3779 WHA **DECLARATION OF DR. LARRY J. KRICKA IN OPPOSITION TO AFFYMETRIX, INC.'S MOTION FOR SUMMARY JUDGMENT OF NONINFRINGEMENT BASED ON THE COURT'S CONSTRUCTION OF THE TERM "DETERMINING THE AMBIENT CONCENTRATIONS"**

I, Larry J. Kricka, declare:

1. I submit this declaration in support of Multilyte Ltd.'s Opposition to Affymetrix Inc.'s Motion for Summary Judgment of Noninfringement Based on the Court's Construction of the Term "Determining the Ambient Concentration." In particular, I have been asked to provide opinions as to whether Affymetrix's products are used to estimate the concentration of a substance in a solution, within the Court's construction of the term "determining the ambient concentrations." I understand that the Court has construed this term to mean "reaching an approximation, rather than an exact calculation, of the amount or activity of a substance in a solution, which is not merely qualitative and is expressed in terms per unit volume, per weight or per parts."

2. One way to estimate the concentration of a substance in a solution is to divide the amount or activity of the substance, A, by the sample volume, V. For multiple samples of uniform volume, however, the volume need no longer be factored into the measurement since it is no longer a variable. In other words, V can be ignored and the concentrations of the substance in the samples can be read directly by the amount or activity measurement, A. In such a circumstance, the expression of A performs the same function, in the same way and with the same result, as the expression of A divided by V.

3. Researchers frequently measure the concentration of an analyte in a sample in terms of its "activity," which can be generally described as the ability of the analyte to undergo or cause certain chemical and/or physical reactions in the assay system. For instance, the concentration of a sugar-degrading enzyme can be estimated by mixing the sample with a sugar solution, and measuring the amount of sugar degrading "activity" that results. In such assays, the activity measurement can be converted to a concentration estimate by dividing the activity by the sample volume, V. For multiple samples of uniform volume, however, V can be ignored and the concentration estimate derived directly from the activity measurement. Again, in such a circumstance, the expression of activity performs the same function, in the same way and with the same result, as the expression of activity divided by V.

4. The concentration of a particular nucleic acid can be measured in terms of its "hybridization activity," *i.e.*, its ability to bind or "hybridize" in the single-stranded state to a

complementary DNA or RNA molecule. Such concentration estimations, based on measurement of the hybridization activity of a sample, are routinely performed by biologists. Generally, the assay is designed such that the probe/target complex formed through hybridization can be quantified by measuring, for example, the fluorescence emitted from a fluorescent "label." The amount of fluorescence detected after hybridization, called the fluorescence intensity, is used as a direct measure of the amount of target nucleic acid in the sample of known volume and hence of the target concentration.

5. As with any assay that measures hybridization activity, Affymetrix's microarrays exploit the ability of a target, single-stranded DNA or RNA molecule to bind or hybridize specifically to its complementary sequence. An Affymetrix microarray consists of thousands of features containing immobilized specific oligonucleotide "probes," each of which is capable of specific binding to a complementary nucleic acid sequence present in the labeled target. The level of hybridization activity between an oligonucleotide probe and its complementary sequence is detected and quantified by measuring the fluorescence intensity generated after hybridization. Affymetrix publications variously refer to this hybridization-generated fluorescence intensity as the "hybridization intensity" or "hybridization signal." Ex. 1 at p. 1677, Ex. 2 at p. 1361.

6. In practice, the target DNA or mRNA is often subjected to amplification before it is hybridized to its specific probe. Under a protocol that Affymetrix provides to its customers, the labeled molecule that actually binds to the oligo probe on the array is not the original target mRNA itself, but instead is a labeled cRNA produced by amplification of the original target mRNA using a process known as "in vitro transcription" ("IVT"). Ex. 3 at pp. 2.1.3-46.

7. The use of a cRNA intermediate is done merely in order to enable better detection of target via amplification of this target during the labeling process. If the target is present in sufficiently large amounts and can be easily labeled, then it is not necessary to amplify the target by IVT. Instead, the target mRNA can be labeled directly and hybridized to the array. Exs. 1, 2.

8. As Wodicka's publication demonstrates, it makes no difference to the investigator whether it is the cRNA intermediate or the original RNA that is labeled and hybridized to the probe, because the hybridization intensity observed using either technique reflects the original

concentration of target mRNA. Ex. 2. The amplification that occurs during cRNA synthesis is quantitative because it preserves the original relationship between target concentration and signal intensity through "reproducible linear amplification of the complete poly $(A)^+$ population," Ex. 2 at p. 1359, such that *the concentration of amplified cRNA remains directly proportional to the concentration of original target mRNA*. This is also confirmed by the Lockhart publication. Ex. 1. Lockhart, like Wodicka, synthesized labeled cRNA from mRNA and hybridized this cRNA to GeneChip arrays. Like Wodicka, he observed that the hybridization signal generated using cRNA was "quantitatively related to the amount of spiked specific poly (A) RNA over the entire concentration range (250-fold) for all five RNAs." Ex. 1 at Table 1. In other words, he used the cRNA fluorescence intensities to measure the target mRNA concentration. This confirms that cRNA can be used in the same way as the original target mRNA to measure the target RNA concentration by means of the hybridization intensity. The use of cRNA to hybridize to the probes performs the same function, in the same way and with the same result, as if the original mRNA itself were hybridized to the probes. Likewise, because the concentration of amplified cRNA is proportional to the concentration of original target mRNA in the sample, the determination of the concentration of a cRNA performs the same function, in the same way and with the same result, as a determination of the concentration of the corresponding mRNA.

9. The scientific literature also independently confirms that labeled intermediates produced by amplification of a target can generally be used to quantify the target concentration by measuring the fluorescence intensity of the amplified intermediate. In a process known as quantitative RT-PCR, for instance, the signal intensity can be used to quantify absolute target concentration in spite of the fact that the target has been subjected to several rounds of amplification before hybridization is performed and the resulting fluorescence intensity is measured. Ex. 4.

10. The nature of the hybridization intensity data obtained using Affymetrix's GeneChip scanner and software is described in an Affymetrix publication entitled "Data Analysis Fundamentals," which is publicly available on Affymetrix's website. Ex. 5. According to this Manual, Affymetrix's software first measures the level of fluorescence generated by hybridization

of each probe to its complementary sequence in terms of the fluorescence intensity, and reports these intensities in terms of arbitrarily defined units. This intensity data is provided in the form of electronic files known as the ".dat" and ".cel" files.

11. Affymetrix also reports a "signal value," which it estimates by correcting the raw intensity for non-specific (background) signal and cross-reactivity. This is done by subtracting the "stray signal," measured by use of a mismatch ("MM") probe, from the raw intensity and then obtaining the statistically averaged difference between perfect match ("PM") and MM intensity across a probe set. Ex. 5 at pp. 44-45. The signal value thus provides "an estimate of the real signal due to hybridization of target." Ex. 5 at pp. 44-45. Thus the signal value, which is nothing more than a measure of fluorescence intensity due to specific hybridization of target to PM probe, provides an estimation of the absolute amount of hybridization activity of target cRNA or mRNA in the sample. In earlier versions of Affymetrix's software, the reported value is the "average difference intensity" or "ADI", but this is essentially the same metric as the later-reported "signal value." The ADI, like the signal value, essentially measures the average difference between PM intensity and MM intensity across a probe set.

12. When the labeled molecule that is contacted with the array and binds to the probe is not actually the original target mRNA molecule, but instead is a labeled cRNA intermediate, the signal value measures the binding activity of the cRNA. Furthermore, as explained in paragraphs 16 through 20, the raw intensity (and thus signal value) of cRNA hybridization still remains quantitatively related to, and thus predicts, the concentration of target mRNA originally present. Both Lockhart and Wodicka use cRNA hybridization intensity to measure concentration of the original mRNA target. Exs. 1, 2.

13. Relative changes in transcript concentration can be measured through another reported value termed the "signal log ratio" ("SLR") derived by "comparing each probe pair on the experiment array to the corresponding probe pair on the baseline array." Ex. 5 at p. 51. The SLR provides a measure of the relative concentration of a transcript as between an "experiment" sample and a "baseline" sample. Ex. 5 at p. 46. A relative measure of concentration is a type of concentration measurement.

14. In addition to the SLR, Affymetrix provides the raw intensity data from each probe, as well as the signal value, which is a non-relative measure that represents the statistically averaged difference between PM and MM intensities for a particular probe set. Ex. 5. As discussed in paragraphs 16 through 29, below, both Affymetrix and non-Affymetrix researchers treat the reported signal value and raw intensity data as absolute concentration measurements, expressed in terms of arbitrary fluorescence units. In addition, the signal value or raw intensity data provides the absolute target concentration in picomoles per liter (pM) through comparison with another RNA, called a “reference” or a “spike,” that is added into the sample at known concentrations.

15. Note that while the volume of the sample is not explicitly factored into the signal value, this signal value nevertheless includes a volume factor. Because the volume of all assays using a particular chip remains the same, the signal value is implicitly expressed per unit volume. For example, as explained in an Affymetrix technical manual that is publicly available on Affymetrix’s website, the volume of the reaction is normally 200 µl for arrays manufactured in Affymetrix’s so-called “standard” format. Ex. 3. Accordingly, every signal value obtained for these arrays is per 200 µl of sample. This is confirmed by scientific publications that measure the “concentration” of a target analyte, including RNA, in terms of its activity, expressed in arbitrary units. Ex. 6. In these publications, the volume is automatically factored into consideration by the fact that the volume remains constant across the experiments. For RNA in particular, the concentration is expressed as a measure of fluorescence intensity expressed in arbitrary units. Ex. 6.

16. The fact that the signal value provides an estimate of the absolute target concentration is further confirmed by peer-reviewed publications by Affymetrix’s own scientists, which report that the two values are linearly related and therefore the signal value can provide an estimate of absolute target concentration. For instance, the Lockhart publication measured the signal produced by hybridization of target to its corresponding probe. Ex.1. Lockhart reported that “[h]ybridization signals are *quantitatively related to target concentration.*” Ex. 1 at Figure 3 (emphasis added). Lockhart also provides a figure that depicts this fact pictorially. Ex. 1 at Figure 3. This graph shows that the log of hybridization intensity (*i.e.*, signal value) varies linearly with

the log of the absolute target concentration, measured in picomoles per unit volume (pM units).

17. Lockhart also explicitly confirms that signal intensity is a concentration measurement by explaining how it is convertible to different kinds of concentration units that are commonly used by biologists. He first explains how signal values can be converted into concentration estimates in terms of "RNA frequency." This measurement reports the frequency of that mRNA in the complex RNA background. For instance, a frequency of 1:3000 for a particular RNA indicates that one molecule of this particular target RNA is present in every 3000 molecules of total cellular RNA in the sample (total cellular RNA consists of a mixture of approximately 15,000 different kinds of mRNA molecules each having a different sequence). RNA frequencies therefore are concentration measurements included within this Court's construction, since they are expressed in terms of amount-per-part or parts-per-part (ppp). According to Lockhart, "*the hybridization intensity is linearly related to RNA target concentrations between 1:300,000 and 1:3000*." Ex. 1 at p. 1677. Lockhart explains that concentration measurements expressed in terms of signal value can converted into terms of RNA frequencies as follows:

> Fluorescence intensities were converted to RNA frequencies by comparison with the signals obtains for a bacterial RNA spiked into the samples at known amounts prior to hybridization. *A signal of 50,000 corresponds to a frequency of approximately 1:100; a signal of 1000 to a frequency of 1:5000; and a signal of 100 to a frequency of 1:50,000.*

Lockhart, Ex. 1 at Figure 4 (emphasis added).

18. Lockhart further explains that concentration estimates from Affymetrix GeneChips that are expressed as RNA frequencies can be easily converted into Molar concentrations and/or absolute amounts as follows: "In 10 ug of total RNA and a volume of 200 µl, a frequency of 1:300,000 corresponds to a concentration of approximately 0.5 pM and 0.1 fmol (approximately 6 x 10^7 molecules or about 30 pg) of specific mRNA." Ex. 1 at p. 1677. Lockhart also often converts signal intensities into concentrations expressed in terms of frequencies ("RNA frequencies are given as the molar amount of an individual RNA per mole of total RNA," Ex. 1 at p. 1677) and then equated those frequencies to "copies per cell." Ex. 1 at p. 1677. "Copies per cell" is a concentration unit that is widely used by biologists and is actually an amount-per-volume-based unit. Here, the cell is acting as a proxy for a certain unit of volume that is occupied by the cell.

This unit of volume ("cell volume") is more relevant for biologists than a metric volume expressed in liters since it conveys more biologically relevant information. The RNA copy number per cell is therefore a concentration measurement, expressed in terms of molecules per unit volume, that falls within the Court's construction. Lockhart explains that: "A frequency of 1:300,000 is that of an mRNA present at about 1 to 3 copies per cell." Ex. 1 at p. 1677.

19. Another Affymetrix publication by Wodicka confirms these results and reports similar observations, reporting that both "*absolute nucleic acid abundance and relative changes* can be determined based on the observed hybridization signals." Ex. 2 at p. 1361. Note that here Wodicka is measuring absolute RNA concentration in terms of "abundance," which is the same as RNA frequency and is a part-per-part estimation. Wodicka, like Lockhart, reports that signal intensity can be converted directly into mRNA concentrations, expressed in terms of copy number per cell: "An intensity of 400-500 corresponds to approximately one copy per cell." Ex. 2 at p. 1360 and p. 1361. This again confirms that signal intensity is itself an estimate of the absolute concentration of target RNA. Ex. 2.

20. Wodicka also reports that absolute concentration measurements obtained using GeneChip arrays are accurate within a 2-fold range of error, which is more than accurate enough to provide biologically useful information. Ex. 2. She explains that the absolute concentration of any particular target mRNA in a cell can range from 0.1 to several hundred copies per cell; in other words, absolute mRNA concentration can vary a thousand-fold, *i.e.*, over a range of three logs. Consequently, an estimation within a 2-fold range of error is sufficient to provide a good estimate of target concentration. Wodicka's results indicate that "a concentration for a given nucleic acid sequence can be assigned as X based on the observed fluorescence intensity with a greater than 95% probability that the actual concentration is between 0.5X and 2X." Ex. 2 at p. 1361. "Taken together, these results indicate that *absolute nucleic acid abundance* and relative changes can be determined based on the observed hybridization signals." Ex. 2 at p. 1361.

21. A third Affymetrix publication in 1999 by Lipshutz again states that "the hybridization signal intensities . . . have been shown to be *directly proportional to RNA concentration*, and are predictive of *absolute RNA concentration* within a factor of two." Ex. 7 at

Table 1 (emphasis added). Lipshutz also cites the Lockhart and Wodicka papers in support of this contention. Affymetrix's Chief Executive Officer and declarant, Stephen Fodor, is also named as an author of this publication. Ex. 7.

22. Affymetrix's publications also explain how to obtain absolute concentration estimates in picomoles per liter by using a reference RNA, or "spike," that is added to the sample at known concentrations. Frequently, biological investigators convert concentration estimates, expressed in terms of arbitrarily defined activity units, into standard concentration units such as picomoles per liter (pM) by constructing a calibration curve, which is obtained by adding to a sample increasing concentrations of a particular RNA, called a "reference" or "spike," and measuring the resulting hybridization signal of the reference RNA for each concentration. Suppose that the hybridization intensity for a reference RNA spike that is added at 1 pM concentration is 200 A.U. (arbitrary units of fluorescence intensity); when added at 2 pM concentration, the spike's intensity is 400 A.U.; at 3 pM concentration, the intensity is 600 A.U., etc. This relationship of reference RNA concentration to hybridization intensity can be graphically represented by plotting RNA concentration on the X axis against signal intensity on the Y axis. Such a graph is termed the "calibration curve," which can be used to infer the absolute concentration of RNA in a test sample from its hybridization intensity. For instance, given the above data, an investigator would infer that another sample containing target mRNA that had a hybridization intensity of 300 A.U. had an absolute concentration of 1.5 pM.

23. I understand that Affymetrix denies the feasibility of this procedure, arguing that it is not possible to infer the absolute concentration, C_1, of an RNA with sequence 1 by comparing its hybridization intensity, I_1, to the hybridization intensity, I_2, obtained from a different "reference" RNA that has been "spiked" or added to the sample at known concentrations. However, Affymetrix's own scientists, Lockhart and Wodicka, both employ precisely this approach and report that such calibration via use of a reference spike works accurately within a 2-fold error range. Exs. 1, 2. Each scientist actually measures the concentration of not just one, but several different test RNAs, by comparing the hybridization intensity for each unknown RNA to the intensity of a reference RNA which is spiked into the sample at known concentrations. Lockhart measures the

absolute concentration (RNA frequency) of five different interleukin mRNAs by comparing their hybridization intensities (measured as the averaged difference of PM and MM signal) to the hybridization intensity of a reference RNA for the bacterial gene known as biotin synthetase. Ex. 1 at Figure 4. He explains that "[f]luorescence intensities were converted to RNA frequencies by *comparison with the signals obtained for a bacterial RNA (biotin synthetase) spiked into the samples at known amounts prior to hybridization.*" Using the spike intensities as a calibration, he concludes that for the test interleukin RNAs, "[a] signal of 50,000 corresponds to a frequency of approximately 1:100." Ex. 1 at Figure 4.

24. Similarly, Wodicka uses both TBP RNA and E. coli and phage control RNAs (Ex. 2, Table 1), which are present in the sample at known concentrations, as calibration references. She measures the intensities of these reference RNAs and infers that "an intensity of 400 to 500 corresponds to approximately 1 copy per cell." Ex. 2 at p. 1360. She then measures the hybridization intensities for over 100 different yeast RNAs and calculates their absolute concentration, in terms of copy number per cell, by comparison with the reference TBP: "Absolute copy numbers were assigned using TBP . . . RNA as a standard, measured by Iyer and Struhl at 3.5 copies per cell." Ex. 2 at p. 1365.

25. Affymetrix in fact explicitly instructs its users to construct a similar calibration curve when performing microarray experiments. It provides customers with a technical manual titled "GeneChip Expression Analysis" ("Expression Manual"), which contains detailed, step-by-step instructions on how to perform experiments using Affymetrix's GeneChips. Ex. 3. In this Manual, Affymetrix recommends that hybridization step should be performed after spiking into the sample known concentrations of four different reference bacterial RNAs, named *lys*, *phe*, *thr* and *dap* respectively. These four RNAs are provided to the user in the form of a "polyA control kit" from Affymetrix. According to the Expression Manual, these four RNAs should be "spiked directly into RNA samples *to achieve the final concentrations*" of 1:100,000; 1:50,000; 1:25,000; and 1:6,667 of *lys*, *phe*, *thr* and *dap* respectively.[1] Ex. 3 at p. 2.1.13. Figure 2.1.3 of the Expression

[1] Here, Affymetrix is expressing concentrations in terms of "ratio of copy number," which is the same unit as RNA frequency used in the Lockhart and Wodicka papers.

Manual *plots the signal intensities of all four spikes against their absolute target concentration* and shows that these are *linearly related*. This figure therefore demonstrates not only that signal intensities *can be compared* across different RNAs and but also that Affymetrix explicitly instructs its users to do so.

26. Figure 2.1.3 of Exhibit 3 also reveals that the reference intensities can in fact be used to construct a calibration curve. It plots the signal intensities of reference RNAs against their concentrations; in other words, Figure 2.1.3 itself is a sample calibration curve that Affymetrix includes in its detailed instructions to its users. As Figure 2.1.3 of the Expression Manual shows, the signal intensity of each probe after hybridization remains linearly related to concentration and can therefore be used to estimate the target concentration of a test RNA. I understand that Affymetrix asserts that the purpose of these 4 spiked transcripts is to act as a control for target labeling. Even if Figure 2.1.3 represents an assay that monitors target labeling, however, its undeniable significance is that the signal obtained after the amplification and labeling process remains quantitatively related to target concentration because the part-to-part relationship does not change. In other words, Figure 2.1.3, even when considered as a depiction of labeling efficiency, leads one of ordinary skill in the art inescapably to the scientific conclusion that the signal intensity remains linearly related to the concentration, and thus that the intensity of the four spiked transcripts *lys*, *phe*, *thr* and *dap* can be used as references that can be compared to the intensity of a target mRNA in order to estimate its concentration. Furthermore, Affymetrix's description of the purpose of its recommended procedure does not change the essential nature of the procedure, which involves measuring the intensity generated by adding known concentrations of "spikes" to a sample. *This is exactly the process that would be performed by a user who desired to construct a concentration calibration curve.* In fact, the use of multiple spike concentrations suggests that the intent behind the process is not to monitor the labeling process (which can be done by spiking in the reference RNAs at a single concentration) but instead is to obtain calibration values of fluorescence intensity generated by a single concentration unit of target (which can only be done if spikes are added in at multiple concentrations).

27. I understand that Affymetrix disputes that signal values provide estimates of

absolute target concentration, arguing that quantitative detection of target concentration via fluorescence signal intensity is not possible because target mRNA is subjected to amplification before hybridization to its probe. As noted above in paragraphs 16 through 20, however, Affymetrix's own scientists have used the hybridization intensity of amplified cRNA to estimate the concentration of target mRNA present in the sample. Exs. 1, 2. Their publications confirm that Affymetrix's "reproducible linear" amplification process (Ex. 2 at p. 1359) is carried out in a quantitative fashion, such that fluorescence intensity remains linearly related to original target concentration despite amplification. In both the Lockhart and Wodicka papers, Exs. 1 & 2, the labeled cRNA was produced by subjecting total poly (A) mRNA to double-stranded cDNA synthesis, followed by amplification using in vitro transcription in the presence of biotin-labeled or fluorescein-labeled nucleotides. Ex. 1, "Experimental protocol"; Ex. 2, "Experimental Protocol." This fact is relevant because it confirms that the target RNA was prepared by the same method that is recommended in Affymetrix's Expression Manual, which describes in detail the protocol for performing GeneChip assays. Ex. 3 at pp. 2.1.3-46.

28. Another publication by Ishii et al. compared the quantitative accuracy of GeneChip arrays with the accuracy of another, widely used method of quantifying target RNA known as "SAGE" (Serial Analysis of Gene Expression). Ex. 8. They used Affymetrix's GeneChips and software to quantify target concentrations. They reported that "these two methods correlated quite well in both *absolute expression analyses* and comparative analyses." Ex. 8 at p. 136. They conclude that "GeneChip technology is reasonably reliable for quantitative analysis of expression profiling . . ." *Id.* This statement has been widely publicized by Affymetrix in its customer literature. Ex. 9.

29. In yet another publication, Held et al. published a 2003 report, the purpose of which is "to compute transcript concentration levels from microarray data" obtained from Affymetrix GeneChips. Ex. 10 at p. 7575. Their aim is to "obtain accurate expression levels from the raw [intensity] data" reported by Affymetrix's software. Ex. 10 at p. 7575. They state that one advantage of Affymetrix GeneChips, as opposed to other microarrays, "is that these chips provide an absolute measure of gene expression (*i.e.*, transcript copies per cell), whereas spotted arrays

typically measure up-or-down regulation relative to some control condition." Ex. 10 at p. 7575. They use the raw intensities provided by Affymetrix as a measure of absolute hybridization intensity. They also predict absolute concentrations estimates from the signal values. Finally, they compare the accuracy of concentration estimations obtained using their own algorithm with estimations using Affymetrix's Microarray Suite 5 (MA5) software, concluding that the accuracy of concentration values predicted by their algorithm and Affymetrix's algorithm is similar. Ex. 10.

30. Similarly, Leemans et al. cite the Lockhart publication and state that "the difference between the perfect match hybridization signal and mismatch signal is proportional to the abundance of a given transcript." They use Affymetrix's GeneChips and software to measure the signal value, which they refer to as "average difference," of each gene and use the signal value to quantitate "relative transcript abundance." Ex. 11 at pp. 12139-40. In another publication, Jain et al. state that "DNA microarrays have come into widespread use to compare expression levels and DNA copy number in biological samples." Ex. 12 at p. 325.

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct. Executed this 7th day of April, 2005 in Baton Rouge, Louisiana.

Larry J. Kricka

LARRY J. KRICKA